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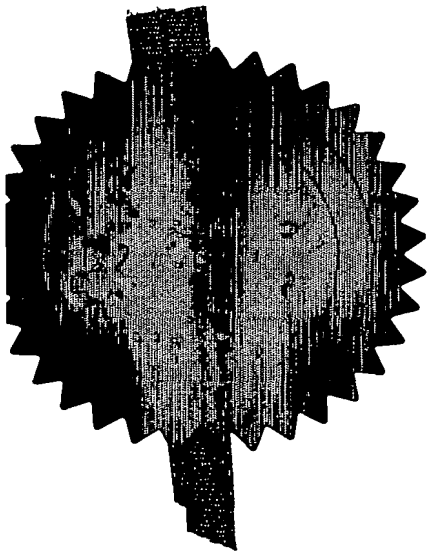

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Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — **UK**

4372348001

4. Title of the invention — **Seal Material for a Dispensing Apparatus**

5. Name of your agent *(if you have one)* — **BOULT WADE TENNANT**

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Seal Material for a Dispensing Apparatus

The present invention relates to a seal material and, in particular, to an elastomeric seal material which may be used in a dispensing apparatus for dispensing pressurised fluid in the form of an aerosol. Such an apparatus may be used for dispensing medicine or products in solution or suspension in an alcohol base.

It is known from GB-1201918 to provide a dispensing apparatus in which pressurised fluid from a pressurised dispensing container is released by a valve in a substantially controlled manner, the valve including elastomeric seals which are annular and which co-operate with a sliding valve stem to open and close fluid ports.

Known rubber compounds for sealing pharmaceutical metered dose aerosol inhalers are based on the traditional technology of vulcanising a synthetic or natural rubber polymer.

The required material properties necessary for good seal performance for pharmaceutical applications include: chemical compatibility (swell), tensile strength, permanent compression set, stress relaxation, elastic modulus, regulatory compliance, low extractives (i.e. cleaner materials), and stable properties after extraction.

Products to be dispensed are commonly provided in solution or suspension in an alcohol base, this being particularly common in the dispensing of medicinal compounds for inhalation therapy.

A typical apparatus includes a CFC volatile propellant having a liquid phase in which the product together with the alcohol carrier is readily soluble within the container. A typical material for the valve seal is a synthetic rubber such as nitrile rubber.

Recent trends in the production of aerosol dispensers have moved away from CFC propellants because of their environmental hazards and HFC propellants are now being introduced. A problem with such propellants is that alcohol is less soluble in the liquid phase of such propellants and tends to separate within the container, thereby exposing the valve seals to a much greater concentration of alcohol than was formerly the case. Seal materials such as nitrile rubber allow alcohol vapour to escape by permeation over extended storage periods so that the remaining quantity of alcohol is significantly depleted.

Accelerators are compounds which reduce the time required for curing/cross-linking of natural and synthetic rubbers. Accelerators may also act to improve the ageing characteristics and other physical properties of the rubber. Known accelerators include sulphenamides, guanidines, thioureas, thiazoles, dithiocarbamates (eg tellurium diethyldithio carbamate), thiuram sulphides (eg dipentamethylene thiuram hexasulphide and tetramethylthiuram disulphide), zinc oxide and tertiary amines.

The most important commercial cure accelerators are the mercaptobenzothiazole derivatives for example MBTS (dibenzthiazyle disulphide). As delayed-action primary accelerators, these derivatives provide good

scorch protection, i.e. resistance to premature cross-linking, especially in polychloroprene rubbers.

Bromobutyl and butyl rubbers may be cured using a sulphur curing agent, together with MBTS and optionally thiuram (TMTD, tetramethyl thiuram disulphide). However, the combination of MBTS and TMTD can lead to the formation of nitrosamines which are undesirable in seals for pharmaceutical applications. The use of MBTS on its own can result in an MBT-type (2-mercaptobenzthiazole) residue as the by-product of the cross linking reaction. Such a residue is undesirable because it can leach out of the sealing material and migrate into the drug media. MBT also has a bitter taste.

Polychloroprene elastomers require accelerators for a practical cure reaction. A known accelerator is 2-mercaptoimidazoline (NA-22). However, there are concerns concerning the toxicity of this accelerator. In addition, this accelerator suffers from scorch, i.e. premature cross-linking. While MBTS and/or TMTD may be used in combination with NA-22 to alleviate such problems, there still exists the problem of undesirable by-product formation.

Peroxides such as dicumyl peroxide can also be used to cure polychloroprene. However, the curing reaction can be variable and this may affect the material properties; in extreme cases, the material can become brittle. Moreover the products of the reaction have to be removed as they can deteriorate Elastomer properties, for example ageing. Another problem is that peroxides are deactivated by antioxidants. Antioxidants are often required to enhance the ageing properties of the elastomer.

In most pharmaceutical applications it is also necessary to extract or wash the cured elastomer in order to remove surface residues and by-products resulting from the cure reaction and moulding process. The aforementioned conventional cure/accelerator systems require relatively lengthy extraction times (typically 50 to 70 hours). Prolonged extraction times have been found to result in a deterioration in material properties.

It is an object of the present invention to provide a seal material for a dispensing apparatus which addresses at least some of the problems associated with the prior art.

Accordingly, in a first aspect the present invention provides a seal for a valve for use in a pharmaceutical dispensing device, which seal is formed from an elastomeric composition comprising:

(a) an isobutylene polymer or co-polymer thereof;

(b) a cross-linking agent for the isobutylene polymer or co-polymer thereof; and

(c) an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof.

The elastomeric composition preferably comprises one or more of polyisobutylene, polybutene, butyl rubber, halogenated butyl rubber, including derivatives thereof. More preferably, the elastomeric composition comprises butyl rubber or bromobutyl rubber. Butyl rubber is a copolymer made from isobutylene and a small amount of a diolefin such as, for example, isoprene (2-methylbuta-1,3-diene).

Typically, butyl rubber comprises approximately 97% isobutylene and approximately 3% isoprene, and it may be polymerized using an aluminium chloride catalyst. Halogenated butyl rubbers such as bromobutyl rubber and chlorobutyl rubber may be made by treating isoprene-isobutylene rubber with bromine/chlorine.

In a second aspect the present invention provides a seal for a valve for use in a pharmaceutical dispensing device, which seal is formed from an elastomeric composition comprising:

(a) a chlorine-substituted diene polymer or co-polymer thereof;

(b) a cross-linking agent for the chlorine-substituted diene polymer or co-polymer thereof; and

(c) an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof.

In the second aspect the elastomeric composition preferably comprises a chlorine-substituted butadiene polymer, more preferably 2-chlorobuta-1,3-diene (i.e. polychloroprene, also known as Neoprene).

In both the first and second aspects the seal may be used in a valve for use in a pharmaceutical dispensing device, such as, for example, a nasal, pulmonary or transdermal delivery device. A preferred use of the seal is in a pharmaceutical metered dose aerosol inhaler device. The term pharmaceutical as used herein is intended to encompass any pharmaceutical, compound, composition, medicament, agent or product which can be delivered or administered to a human being or animal, for example pharmaceuticals, drugs, biological and medicinal

products. Examples include antiallergics, analgesics, bronchodilators, antihistamines, therapeutic proteins and peptides, antitussives, anginal preparations, antibiotics, anti-inflammatory preparations, hormones, or sulfonamides, such as, for example, a vasoconstrictive amine, an enzyme, an alkaloid, or a steroid, including combinations of two or more thereof. In particular, examples include isoproterenol [alpha-(isopropylaminomethyl) protocatechuyl alcohol], phenylephrine, phenylpropanolamine, glucagon, adrenochrome, trypsin, epinephrine, ephedrine, narcotine, codeine, atropine, heparin, morphine, dihydromorphinone, ergotamine, scopolamine, methapyrilene, cyanocobalamin, terbutaline, rimiterol, salbutamol, flunisolide, colchicine, pirbuterol, beclomethasone, orciprenaline, fentanyl, and diamorphine, streptomycin, penicillin, procaine penicillin, tetracycline, chlorotetracycline and hydroxytetracycline, adrenocorticotropic hormone and adrenocortical hormones, such as cortisone, hydrocortisone, hydrocortisone acetate and prednisolone, insulin, cromolyn sodium, and mometasone, including combinations of two or more thereof.

The pharmaceutical may be used as either the free base or as one or more salts conventional in the art, such as, for example, acetate, benzenesulphonate, benzoate, bircarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, fluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulphate, mucate, napsylate, nitrate, pamoate,

(embonate), pantothenate, phosphate, diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, and triethiodide, including combinations of two or more thereof. Cationic salts may also be used, for example the alkali metals, e.g. Na and K, and ammonium salts and salts of amines known in the art to be pharmaceutically acceptable, for example glycine, ethylene diamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 1-amino-2-propanol-amino-2-(hydroxymethyl)propane-1,3-diol, and 1-(3,4-dihydroxyphenyl)-2 isopropylaminoethanol.

The pharmaceutical will typically be one which is suitable for inhalation and may be provided in any suitable form for this purpose, for example as a powder or as a solution or suspension in a solvent or carrier liquid, for example ethanol.

The pharmaceutical may, for example, be one which is suitable for the treatment of asthma. Examples include salbutamol, beclomethasone, salmeterol, fluticasone, formoterol, terbutaline, sodium chromoglycate, budesonide and flunisolide, and physiologically acceptable salts (for example salbutamol sulphate, salmeterol xinafoate, fluticasone propionate, beclomethasone dipropionate, and terbutaline sulphate), solvates and esters, including combinations of two or more thereof. Individual isomers such as, for example, R-salbutamol, may also be used. As will be appreciated, the pharmaceutical may comprise of one or more active ingredients, an example of which is flutiform, and may optionally be provided together with a suitable carrier, for example a liquid carrier. One or more surfactants may be included if desired.

In both the first and second aspects the cross-linking agent (also known as a curing agent) provides or facilitates network formation to result in a three-dimensional polymer network structure. The cross-linking agent may act by reacting with the functional groups on the polymer chain. The cross-linking agent will typically comprise sulphur or a sulphur-containing compound. The cross-linking agent is preferably substantially free of any peroxide curing agents such as, for example, dicumyl peroxide.

In both the first and second aspects the polysulphide compound is preferably derived from a substituted xanthic acid or derivative thereof, preferably of the type ROC(S)SH, in which R is typically an alkyl radical. The substituted group in the polysulphide compound typically comprises an isopropyl group.

The polysulphide compound preferably comprises three or more bridging sulphur atoms, more preferably 3, 4 or 5 bridging sulphur atoms.

The polysulphide compound is preferably substantially free from nitrogen, phosphorus and metallic elements.

Advantageously, the polysulphide compound comprises or consists of diisopropyl xanthogen polysulphide.

In both the first and second aspects the elastomeric composition typically comprises up to 3 wt.% of the accelerator based on the total weight of the accelerator and polymer in the composition, more typically up to 1.5 wt.% of the accelerator based on

the total weight of the accelerator and polymer in the composition, still more typically up to 1 wt.% of the accelerator based on the total weight of the accelerator and polymer.

In both the first and second aspects the weight ratio of the accelerator to the cross-linking agent in the elastomeric composition is preferably in the range of from 1:1 to 3:1, more preferably from 1:1 to 2:1.

In both the first and second aspects the seal advantageously further includes a filler, preferably a mineral filler. Mineral fillers are preferable to carbon black in order to minimise the formation of polynuclear aromatic hydrocarbon compounds. Suitable examples include any of magnesium silicate, aluminium silicate, silica, titanium oxide, zinc oxide, calcium carbonate, magnesium oxide magnesium carbonate, magnesium aluminium silicate, aluminium hydroxide, talc, kaolin and clay, including combinations of two or more thereof. Preferably, the filler is or comprises one or more of magnesium silicate, talc, calcined clay, and/or kaolin.

In both the first and second aspects the seal further preferably further includes a process aid, preferably a low molecular weight polyethylene.

In both the first and second aspects the seal may further comprise any of a reinforcement agent, a plasticizer, a binder, a stabilizer, a retarder, a bonding agents, an antioxidant, a lubricant, a pigment, a wax, a resin, an antiozonants, a secondary accelerator or an activator, including combinations of two or more thereof. Examples of antioxidants are 2:2′-methylene-bis(6-(1-methyl-cyclohexyl)-para-

creosol) and octylated diphenylamine. An advantage of the seal according to the present invention is that it can be essentially free of an antioxidant if desired.

It will be appreciated that certain constituents may have more than one effect. For example, zinc oxide may act as an activator and as a filler. Similarly, magnesium oxide may act as an acid absorber and as a filler.

The term seal as used herein is intended to encompass any sealing member or portion thereof present in a pharmaceutical dispensing device, including, but not limited to, gaskets and seals whether static or dynamic.

The present invention also provides a valve for use in a pharmaceutical dispensing device and having a seal as herein described with reference to either the first or second aspect of the invention.

It will be appreciated that the seal may be provided as a separate component or may be formed integrally with the valve.

The present invention also provides a pharmaceutical dispensing device having a valve as herein described. The pharmaceutical dispensing device may be, for example, a nasal, pulmonary or transdermal delivery device. A preferred device is a pharmaceutical metered dose aerosol inhaler device.

The present invention also provides a dispensing apparatus for dispensing pressurised fluid comprising a valve body defining a chamber, a valve member extending movably through the chamber and through at least one annular seal co-operating with the valve

member and the body to regulate the discharge of fluid, wherein the or at least one of the seals is as herein described with reference to either the first or second aspect of the invention.

Such a device may be used for dispensing medicine, pharmaceuticals, biological agents, drugs and/or products in solution or suspension.

In a preferred embodiment, the dispensing apparatus comprises a pressurised dispensing container having a valve body provided with two annular valve seals through which a valve member is axially slidable, the seals being disposed at inlet and outlet apertures of a valve chamber so that the valve functions as a metering valve.

The dispensing apparatus as herein described may comprise a pressurised dispensing container operatively connected to the valve body and containing the fluid to be dispensed and a hydrofluorocarbon propellant comprising propellant type 134a or 227. The designation of propellant types referred to in the present application is as specified in British Standard BS4580:1970 "Specification for number designations of organic refrigerants". Accordingly, propellant 134a is: 1,1,1,2-tetrafluoroethane CH_2F-CF_3 and propellant 227 is: 1,1,1,2,3,3,3 heptafluoropropane $CF_3-CHF-CF_3$.

The fluid to be dispensed typically comprises a liquid or particulate product as a solution or suspension in a carrier liquid. The carrier liquid preferably comprises an alcohol such as ethanol. One or more surfactants may be present.

The present invention provides particularly

favourable results when used in conjunction with a hydrofluorocarbon propellant in the aerosol device.

The present invention also provides a seal for a valve for use in a pharmaceutical dispensing device, which seal comprises a vulcanisate of an isobutylene polymer or co-polymer thereof, a cross-linking agent for the isobutylene polymer or co-polymer thereof, and an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof.

The present invention also provides a seal for a valve for use in a pharmaceutical dispensing device, which seal comprises a vulcanisate of a chlorine-substituted diene polymer or co-polymer thereof, a cross-linking agent for the chlorine-substituted diene polymer or co-polymer thereof, and an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof.

In relation to the first aspect, the present invention also provides a process for the preparation of a seal for a valve for use in a pharmaceutical dispensing device, the process comprising:

(i) forming a composition comprising a mixture of an isobutylene polymer or co-polymer thereof, a cross-linking agent for the isobutylene polymer or co-polymer thereof, and an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof;

(ii) initiating a cross-linking reaction in the mixture to form a cross-linked elastomeric composition; and

(iii) either before or after (ii) forming the composition into a seal.

In relation to the second aspect, the present invention also provides a process for the preparation of a seal for a valve for use in a pharmaceutical dispensing device, the process comprising:

(i) forming a composition comprising a mixture of a chlorine-substituted diene polymer or co-polymer thereof, a cross-linking agent for the chlorine-substituted diene polymer or co-polymer thereof, and an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof;

(ii) initiating a cross-linking reaction in the mixture to form a cross-linked elastomeric composition; and

(iii) either before or after (ii) forming the composition into a seal.

In both of the above-described processes the step of forming the composition into a seal may involve one or more forming techniques such as compression moulding, injection moulding and/or extrusion.

The initiation of the cross-linking reaction may be achieved by any of the known conventional techniques, for example heating the formulation to at least the curing reaction temperature, which is typically in the range of from 130 to 200°C.

The use of the accelerator as herein described in the elastomeric compositions according to the present invention can eliminate the need for free sulphur in the cross-linking process. The accelerator as herein described is preferably provided as a liquid and is

preferably miscible with the polymer to provide a homogeneous dispersion. It has been found that the use of such an accelerator facilitates filler dispersion and can obviate the need for a separate plasticiser. The presence of plasticisers is undesirable in that they tend to leach out of the material. In contrast, the accelerator as herein described forms or is part of the cross-linked network and therefore does not leach out into the drug media.

In the seal compositions according to the present invention the accelerator is typically almost totally consumed during the cross-linking reaction. This results in a cleaner rubber and the extractables are reduced. Typically, substantially no nitrosamines are generated during the cross-linking reaction. Furthermore, the compositions according to the present invention show improved ageing characteristics compared with conventional Neoprene and Butyl rubber formulations. Most or substantially all of any by products resulting from the cross-linking reaction may be volatiles.

The present invention will now be further described with reference to the following non-limiting examples and drawings, provided by way of example, in which:

Figure 1 is a plot of ageing at 110°C for Example EF147 (a polychloroprene formulation according to the present invention) compared with a conventional polychloroprene (EF134);

Figure 2 is a plot of ageing at 150°C for Example EF147 (a polychloroprene formulation according to the present invention) compared with a conventional polychloroprene(EF134); and

Figure 3 is a plot of ageing at 130°C for Example EF147 (a polychloroprene formulation according to the present invention) compared with a conventional polychloroprene.

Table 1

Ingredients	Formulation						
	EF147	EF134	EF150(14B)	EF151(14A)	EF149	EF152	EFMBTS
Bromobutyl	0	0	100	100	100	100	100
Polychloroprene	100	100	0	0	0	0	0
Clay	40	40	40	40	30	30	30
Talc	30	30					
Platey Talc			80	80	80	80	80
Stearic Acid	1	1	1	1	1	1	1
Octaamine	0	1	0	0	0	0	0
Antioxidant	1	1	0	0	0	0	0
Robac AS100	1	0	1	1	1.5	2	0
MBTS	0	0	0	0	0	0	2
DPG	0	0	0.5	0	0.5	0	0
TBBS (PM 75%)	0	0	0	1.33	0	0	0
DOTG	0.5	0	0	0	0	0	0
Sulphur	0.5	0	0.5	0.5	0.75	0.75	0.75
Peroxide	0	4	0	0	0	0	0
MgO	4	4	0	0	0	0	0
ZnO	5	5	3	3	5	5	5
Low MW PE	0	0	2	2	2	2	2

Table 2

Ingredients	Formulation									
	EF125	EF126	EF127	EF128	EF129	EF130	EF131	EF132	EF133	EF135
Polychloroprene	100	100	100	100	100	100	100	100	100	100
Clay	40	40	40	50	40	40	40	40	40	30
Talc	40	40	40	30	40	40	40	50	40	30
Stearic Acid	0	0	0	0	0	1	1	0	1	1
Peroxide	6	6	5.5	6	6	6	5	5	5	4
MgO	4	4	0	0	4	0	4	0	4	4
ZnO	5	5	5	5	5	5	5	5	5	5

Key

EF147: Neoprene with sulphur/diisopropyl xanthogen polysulphide cure system (invention)

EF125 - EF135: Neoprene with peroxide cure system (comparative)

EF150 (14B): Bromobutyl rubber with sulphur/diisopropyl xanthogen polysulphide cure system (invention)

EF151 (14A): Bromobutyl rubber with sulphur/diisopropyl xanthogen polysulphide cure system (invention)

EF149: Bromobutyl rubber with sulphur/diisopropyl xanthogen polysulphide cure system (invention)

EF152: Bromobutyl rubber with sulphur/diisopropyl xanthogen polysulphide cure system (invention)

EFMBTS: Bromobutyl rubber with sulphur/MBTS cure system (comparative)

Bromobutyl:	Exxon 2246
Polychloroprene:	Neoprene W
Clay:	Polestar 200R
Talc:	Magsil 2628
Platey talc:	Mistron Vapour RP6D
Robac AS100:	A diisopropyl xanthogen polysulphide available from Robinson Brothers Ltd.
MBTS:	bis(2-benzothiazoyle disulphide) (rubber accelerator)
DPG:	diphenylguanidine (rubber accelerator)- Ekaland DPG Pd (Powder)
TBBS:	N-tertiary butyl 2 benzothiazoyle sulfonamide Robac TBBS (75% active polymer master batch)
DOTG:	di-o-tolylguanidine (rubber accelerator) - Ekaland DOTG Pd (Powder)
Sulphur:	AKM 300# GSS 2.5% (magnesium coated sulphur)
Peroxide:	40% di(2-tert-butylperoxyisopropyl-2-benzene, bis peroxide) - Luperco / Peroximon / Perkadox
Magnesium Oxide:	Maglite Y or DE
Low MW PE:	PE AC617A or Luwax

The rubber formulations were mixed using a Francis Shaw 1.2 l laboratory Banbury Mixer using speed setting 1 (long rotor speed 117 rpm), a friction ratio 1:1.125, and cooling waters circulated through the body, jacket and rotors. Mixing quality and consistency may be controlled by the time of mixing,

the temperature of mixing and the energy used.

Table 3

	EF147	EF134	EF150 14B	EF151 14A	Black nitrile
Acetone extracts	<2%	4.2%	<2%	<2%	8.5-10%
HPLC	No DOTG above limit of 0.005%	Will be peroxide residues by GC-MS	No DPG above limit of 0.005%	MBT detected at 0.007%	N/a
HPLC	N/a	N/a	N/a	N/a	MBT, ZDMC detected at various levels
nitrosamine ppb	N/a	N/a	N/a	N/a	Various levels 17,83
nitrosamine ppb	N/a	N/a	None detected	1	N/a

Table 4

Formulation	Cure Temp	T90 Time to 90% cure min-secs	Hardness	Tensile Strength (MPa)	% EB
EF149	160°C	4.05	54	5.57	432
EF152	160°C	2.49	60	7.62	469
EFMBTS	160°C	3.42		6.59	573

Discussion

1. With reference to Table 3, the acetone extracts in respect of the formulations according to the invention are lower than black nitrile.

2. With reference to formulations EF147, EF150 and EF151, the Robac AS100 concentration is so small that it is not detected by HPLC. The accelerator is therefore almost totally consumed during the cross-linking reaction with the corollary of a cleaner rubber.

3. The acetone extracts for the formulations containing Robac AS100 (i.e. EF147, EF150(14B), and EF151(14A)) are approximately half those obtained for the non-Robac AS100 cured material (i.e. EF134). EF147 and EF134 are polychloroprene compositions differing only in the type of crosslinking system. EF147 has half the acetone extract.

4. With reference to Table 4, the formulation EF152 gave a satisfactory rate of cure even in the absence of a secondary accelerator.

5. With reference to Table 4, the physical properties of the formulations according to the invention are not affected by the use of the Robac AS100 accelerator. Compared with MBTS, the EF152 formulation gave a shorter T90 time.

6. With reference to Table 3 and the formulations according to the invention (i.e. EF149, EF150 and EF151), no nitrosamines were generated.

7. With reference to Figures 1 to 3, the neoprene formulations according to the invention show improved ageing characteristics compared with the comparative formulations.

CLAIMS:

1. A seal for a valve for use in a pharmaceutical dispensing device, which seal is formed from an elastomeric composition comprising:

(a) an isobutylene polymer or co-polymer thereof;

(b) a cross-linking agent for the isobutylene polymer or co-polymer thereof; and

(c) an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof.

2. A seal as claimed in claim 1, wherein the elastomeric composition comprises one or more of polyisobutylene, polybutene, butyl rubber, halogenated butyl rubber, including derivatives thereof.

3. A seal as claimed in claim 2, wherein the elastomeric composition comprises bromobutyl rubber and/or chlorobutyl rubber, including derivatives thereof.

4. A seal for a valve for use in a pharmaceutical dispensing device, which seal is formed from an elastomeric composition comprising:

(a) a chlorine-substituted diene polymer or co-polymer thereof;

(b) a cross-linking agent for the chlorine-substituted diene polymer or co-polymer thereof; and

(c) an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof.

5. A seal as claimed in claim 4, wherein the elastomeric composition comprises a chlorine-substituted butadiene polymer.

6. A seal as claimed in claim 5, wherein the elastomeric composition comprises 2-chlorobuta-1,3-diene.

7. A seal as claimed in any one of the preceding claims, wherein the cross-linking agent comprises sulphur or a sulphur-donating compound.

8. A seal as claimed in any one of the preceding claims, wherein said polysulphide compound is derived from a substituted xanthic acid or derivative thereof.

9. A seal as claimed in any one of the preceding claims, wherein the substituted group in said polysulphide compound comprises or consists of an isopropyl group.

10. A seal as claimed in any one of the preceding claims, wherein said polysulphide compound comprises or consists of diisopropyl xanthogen polysulphide.

11. A seal as claimed in any one of the preceding claims, wherein said polysulphide compound comprises three or more bridging sulphur atoms.

12. A seal as claimed in any one of the preceding claims, wherein said polysulphide compound is substantially free from nitrogen, phosphorus and metallic elements.

13. A seal as claimed in any one of the preceding claims, wherein the elastomeric composition comprises up to 3 wt.% of the accelerator based on the total weight of the accelerator and polymer in the composition.

14. A seal as claimed in claim 13, wherein the elastomeric composition comprises up to 1.5 wt.% of the accelerator based on the total weight of the accelerator and polymer in the composition.

15. A seal as claimed in any one of the preceding claims, wherein the weight ratio of the accelerator to the cross-linking agent in the elastomeric composition is in the range of from 1:1 to 3:1.

16. A seal as claimed in any one of the preceding claims, wherein the seal further includes a mineral filler.

17. A seal as claimed in claim 16, wherein the mineral filler is selected from one or more of magnesium silicate, aluminium silicate, silica, titanium oxide, zinc oxide, calcium carbonate, magnesium oxide magnesium carbonate, magnesium aluminium silicate, aluminium hydroxide, talc, kaolin and clay.

18. A seal as claimed in any one of the preceding claims, wherein the seal further includes a process aid, preferably a low molecular weight polyethylene.

19. A seal as claimed in any one of the preceding claims, further comprising one or more of a reinforcement agent, a plasticizer, a binder, a

stabilizer, a retarder, a bonding agents, an antioxidant, a lubricant, a pigment, a wax, a resin, an antiozonants, a secondary accelerator or an activator.

20. A valve for use in a pharmaceutical dispensing device having a seal as defined in any one of claims 1 to 19.

21. A pharmaceutical dispensing device having a valve as claimed in claim 20.

22. A pharmaceutical dispensing device as claimed in claim 21 which is a pharmaceutical metered dose aerosol inhaler device.

23. A dispensing apparatus for dispensing pressurised fluid comprising a valve body defining a chamber, a valve member extending movably through the chamber and through at least one annular seal co-operating with the valve member and the body to regulate the discharge of fluid, wherein the or at least one of the seals is as defined in any one of claims 1 to 19.

24. A dispensing apparatus which comprises a pressurised dispensing container having a valve body provided with two annular valve seals through which a valve member is axially slidable, said seals being disposed at inlet and outlet apertures of a valve chamber so that the valve functions as a metering valve, wherein at least one of the annular valve seals is as defined in any one of claims 1 to 19.

25. A dispensing apparatus as claimed in claim 23 or claim 24, comprising a pressurised dispensing container operatively connected to the valve body and

containing the fluid to be dispensed and a hydrofluorocarbon propellant comprising propellant type 134a or 227.

26. A dispensing apparatus as claimed in any one of claims 23 to 25, wherein the fluid to be dispensed comprises a liquid or particulate product as a solution or suspension in a carrier liquid comprising alcohol.

27. A dispensing apparatus as claimed in claim 26, wherein the alcohol comprises ethanol.

28. A seal for a valve for use in a pharmaceutical dispensing device, which seal comprises a vulcanisate of an isobutylene polymer or co-polymer thereof, a cross-linking agent for the isobutylene polymer or co-polymer thereof, and an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof.

29. A seal for a valve for use in a pharmaceutical dispensing device, which seal comprises a vulcanisate of a chlorine-substituted diene polymer or co-polymer thereof, a cross-linking agent for the chlorine-substituted diene polymer or co-polymer thereof, and an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof.

30. A process for the preparation of a seal for a valve for used in a pharmaceutical dispensing device, the process comprising:

(i) forming a composition comprising a mixture of an isobutylene polymer or co-polymer thereof, a

cross-linking agent for the isobutylene polymer or co-polymer thereof, and an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof;

(ii) initiating a cross-linking reaction in the mixture to form a cross-linked elastomeric composition; and

(iii) either before or after (ii) forming the composition into a seal.

31. A process for the preparation of a seal for a valve for use in a pharmaceutical dispensing device, the process comprising:

(i) forming a composition comprising a mixture of a chlorine-substituted diene polymer or co-polymer thereof, a cross-linking agent for the chlorine-substituted diene polymer or co-polymer thereof, and an accelerator for the cross-linking agent, wherein the accelerator includes a polysulphide compound derived from a substituted dithiocarbonic acid or derivative thereof;

(ii) initiating a cross-linking reaction in the mixture to form a cross-linked elastomeric composition; and

(iii) either before or after (ii) forming the composition into a seal.

32. A process as claimed in claim 30 or claim 31, wherein the step of forming the composition into a seal involves one or more forming techniques selected from compression moulding, injection moulding and extrusion.

33. A seal for a dispensing apparatus substantially as hereinbefore described with reference to any one of the Examples.

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